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Modulation of the Stress Response by Ethanol in the Rat Frontal Cortex

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HEGARTY, A. A. AND W. H. VOGEL. *Modulation of the stress response by ethanol in the rat frontal cortex.* PHARMACOL BIOCHEM BEHAV 45(2) 327–334, 1993.—Microdialysis was used to characterize the effects of two doses of ethanol, stress, and their interaction on the dopaminergic system. Saline-treated animals showed no changes in levels of dopamine (DA) or dihydroxyphenylacetic acid (DOPAC). Neither a 0.5- nor a 2-g/kg IP injection of ethanol had an effect on DA or DOPAC in resting animals. Immobilization caused marked increases in DA levels and smaller increases in DOPAC. Pretreatment with 0.5 g/kg ethanol did not reduce the stress-induced increase in DA or DOPAC. However, pretreatment with 2 g/kg ethanol strongly reduced and antagonized the stress-induced increases in DA and potentiated the stress-induced increase in extracellular DOPAC. Our data show that ethanol can have different, dose-dependent effects in resting vs. stressed animals, that it has different effects on DA and DOPAC, and that the high dose antagonized stress-induced increases in DA. The latter adds biochemical evidence to the tension-reduction hypothesis of ethanol by perhaps implicating a reduction in the DA stress response by ethanol as a contributing factor in the development of alcoholism.

Microdialysis Stress Immobilization Ethanol Dopamine DOPAC Frontal cortex

MANY studies using microdissection and postmortem analysis have found that stressful stimuli such as electric shock and restraint activate mesocortical dopamine (DA) neurons (7,37,38). Specifically, stress will cause a decrease in whole tissue levels of DA and an increase in tissue levels of its metabolite dihydroxyphenylacetic acid (DOPAC) in the frontal cortex (7,37,38). Using similar techniques, acute administration of ethanol in resting animals does not appear to have a significant effect on cortical tissue levels of DA or DOPAC (13,23). These data would suggest that, unlike stress, acute ethanol does not affect mesocortical DA neurons.

Recently, several investigations using in vivo microdialysis demonstrated that stress causes significant increases in extracellular levels of DA in the frontal cortex (1,21,22), verifying the activation of the mesocortical dopaminergic system by stress. However, to the best of our knowledge no one has used microdialysis to investigate the effects of systemically administered ethanol on DA neurons in the frontal cortex.

It has been proposed that ethanol may antagonize the effects of stress in the CNS, thus making ethanol consumption an alternate coping response to stress that could lead to a vicious cycle ending in alcoholism. Since Cappell and Herman (4) outlined the tension-reduction hypothesis of ethanol consumption, a few studies using postmortem analysis techniques have shown an interaction between ethanol and stress on the dopaminergic system (12,14,15). In these studies, it was found that an acute dose of ethanol can attenuate stress-induced changes in DA in the frontal cortex. However, this interaction of ethanol and stress has not yet been investigated with the more sensitive technique of microdialysis.

To assess the effects of ethanol alone and its interaction with stress, we used microdialysis to determine the effects of immobilization stress and acute ethanol administration alone and in combination on extracellular DA and DOPAC in the frontal cortex of the rat.

METHOD

Animals

Male Sprague-Dawley rats weighing 300–350 g (Zivic-Miller) were maintained in light-, temperature-, and humidity-controlled rooms on a 12 L : 12 D cycle. Food and water were available ad lib.

Surgery and Dialysis

Bilateral dialysis probe cannulae (10 mm long) were implanted during surgery under ketamine with acepromazine and sodium pentobarbital anesthesia in a Kopf stereotaxic frame (Kopf, Topanga, CA). The following coordinates relative to bregma were used for implantation in the frontal cortex: AP +3.2, ML ±1.2, DV −1.5. Animals were allowed at least 48 h to recover from surgery. On the day of the experiment, a Ringer's solution composed of 145 mM NaCl, 2.7 mM KCl,

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1.0 mM $MgCl_2$, 1.2 mM $CaCl_2$, and 0.2 mM ascorbate in a 2 mM phosphate buffer (pH 7.4) (28) was perfused through a concentric microdialysis probe at a flow rate of 2.75 μl/min. Microdialysis probes (tip length 4 mm, tip diameter 0.2 mm) were constructed as described previously (16,19). Cellulose membranes with a molecular weight cutoff of 6,000 (Spectrapor, Fisher Scientific, Pittsburgh, PA) were used in the construction of all microprobes. All experiments were carried out between 0900 h and 1600 h. After rats were sacrificed, brains were inspected to confirm the correct placement of the probe in the frontal cortex.

High-performance Liquid Chromatography Analysis of Dialysis Samples

Samples were collected every 20 min and analyzed immediately thereafter using high-performance liquid chromatography (HPLC) in conjunction with coulometric electrochemical detection. A DuPont C-18 reverse-phase column (4.6 mm i.d. × 25 cm) was used with a mobile phase consisting of 0.120 M citrate, 0.110 M sodium acetate, 4.9 mM heptane sulfonic acid, 0.39 mM EDTA, and 15% methanol. A 20-μl aliquot was assayed for DA and DOPAC with an ESA 5100A coulometric detector (guard cell: −0.20; detector 1: +0.20; detector 2: −0.05). The detection limit of the assay was 0.5 pg/20 μl.

Verification of Neuronal Response With Potassium

After a stable baseline had been reached (approx. 1–2 h), the cortex was perfused with an isoosmotic 100 mM KCl Ringer's solution for 20 min according to the technique developed by Carrozza et al. (6). Potassium-induced release was used as an indicator of functionally active DA terminals in contact with the dialysis membrane (6). If the overflow of DA was approximately three times the basal level of DA seen prior to perfusion with the K^+ solution, the experiment was continued. If DA overflow remained unchanged after K^+ perfusion, the experiment was terminated. An experiment was continued following a K^+ response only after a stable baseline was obtained for several consecutive samples (approx. 90 min).

Experimental Procedures

Rats were divided into six groups. One group (n = 6) received an IP injection of saline vehicle equivalent to 2 g/kg ethanol. The second and third groups were given either a 0.5-g/kg (n = 6) or 2-g/kg (n = 7) 20% v/v IP injection of ethanol, respectively. A fourth group (n = 7) of animals was immobilized in a prostrate position on the laboratory bench as described previously (12) for 40 min. The fifth group (n = 6) was given a 0.5-g/kg IP injection of ethanol 20 min prior to being immobilized for 40 min and the sixth group (n = 7) was given a 2-g/kg IP injection of ethanol 20 min prior to immobilization.

Statistical Analysis

Data were analyzed with a SAS/STAT (SAS Institute, Cary, NC) General Linear Models procedure consisting of a two-way repeated-measures analysis of variance of sample time and treatment followed by a Student-Newman-Keuls posthoc test for a comparison of means. Due to unusually high SDs, data were only marginally statistically significant; therefore, log transformations of the data were carried out to reduce variability between subjects. Data are not corrected for probe recovery.

RESULTS

The average baseline concentrations of DA and DOPAC obtained in cortical dialysate are 2.56 ± 1.2 and 50.12 ±

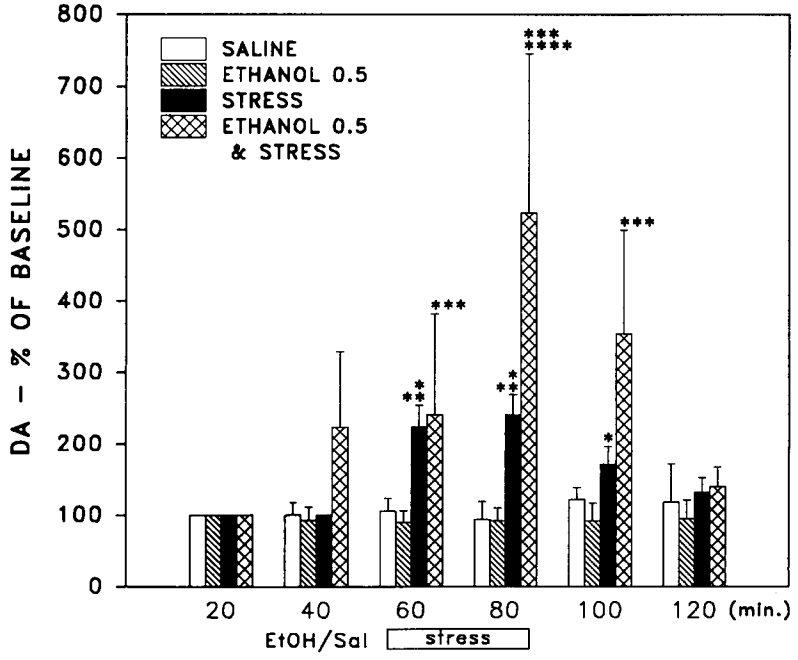

FIG. 1. Effect of 0.5 g/kg IP ethanol in resting and/or stressed rats on cortical dopamine (DA). Results are expressed as the mean ± SEM percent variation of the prestress value. *p < 0.05 vs. ethanol 0.5; **p < 0.005 vs. saline; ***p < 0.04 vs. ethanol 0.5; ****p < 0.004 vs. saline.

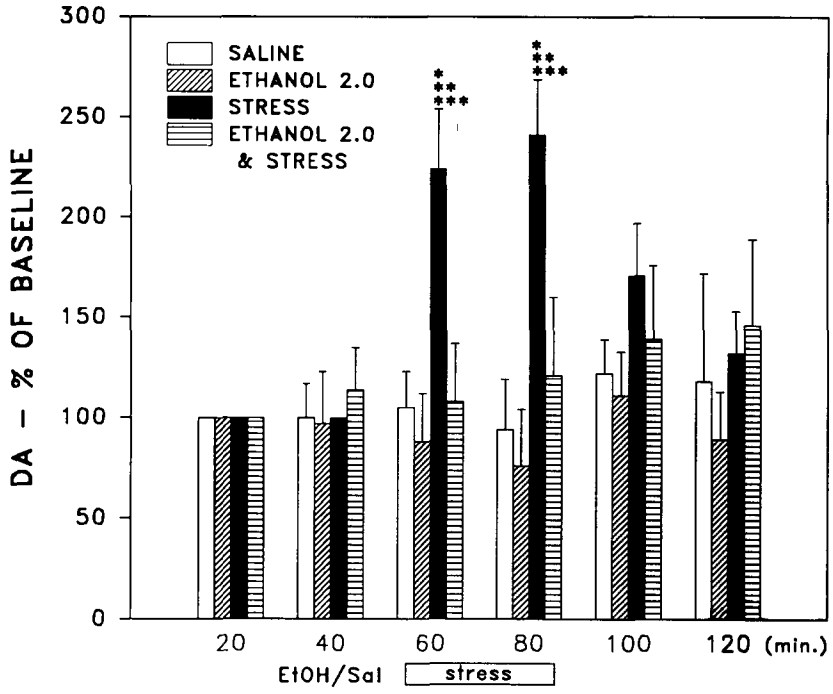

FIG. 2. Effect of 2 g/kg IP ethanol in resting and/or stressed rats on cortical dopamine (DA). Results are expressed as the mean ± SEM percent variation of the prestress value. *$p < 0.005$ vs. saline; **$p < 0.01$ vs. ethanol 2.0; ***$p < 0.01$ vs. ethanol 2.0 and stress.

30.7 pg/20 μl, respectively. The average concentration of DA is similar to previously reported values while that of DOPAC is somewhat lower than some previously reported values (1).

A low dose of ethanol (0.5 g/kg) given to a resting animal did not affect DA (Fig. 1). However, immobilization stress produced significant increases in extracellular DA. DA increased 124% relative to baseline after the first 20 min of immobilization and 141% after 40 min of immobilization. Both of these time points were significantly different from the corresponding control group and a significant time × treatment interaction was found between the stress and saline groups, $F(5) = 8.35$, $p < 0.0001$. Administration of 0.5 g/kg ethanol prior to immobilization significantly increased extracellular DA during stress. After 40 min of immobilization, DA increased 424% relative to baseline, a significant change over both the saline- and ethanol-treated controls, $F(5) = 3.36$, $p = 0.01$. Although it appears that 0.5 g/kg ethanol potentiated the stress response, the effects of the combined treatments were not significantly different from stress alone due to the wide range of responses seen in animals receiving the low dose of ethanol prior to stress.

A high dose of ethanol (2 g/kg) given to resting rats did not affect extracellular DA (Fig. 2) and, again, stress alone caused the expected rise in DA. The same dose administered 20 min before immobilization antagonized and eliminated the increase in extracellular DA produced by stress alone. Extracellular DA was significantly reduced during stress by 2 g/kg ethanol administered prior to immobilization; also, a significant time × treatment interaction, $F(5) = 6.98$, $p = 0.0001$, was found between the stress and the 2-g/kg ethanol-stress treatment groups.

A comparison of the two doses of ethanol is shown in Fig. 3. The high dose of ethanol apparently had the opposite effect of the low (0.5 g/kg) dose of ethanol. The 2-g/kg ethanol-stress treatment group had significantly lower levels of DA than the 0.5-g/kg combined treatment group 40 min after stress, $F(1) = 10.21$, $p = 0.009$. A significant time × treatment interaction was found between the two groups, $F(5) = 2.48$, $p = 0.04$.

The 0.5-g/kg dose of ethanol did not change extracellular DOPAC at any given time point (Fig. 4). However, extracellular DOPAC increased significantly as a result of immobilization stress with a peak 53% greater than baseline 20 min after immobilization, $F(1) = 5.46$, $p = 0.04$. The increase in DOPAC produced by stress was only significantly greater than the saline controls at 100 min. Due to the small number of data points available for the saline-treated group at 120 min, statistical comparisons vs. the saline group were not carried out for this time point. When 0.5 g/kg ethanol was given prior to immobilization stress, DOPAC increased significantly at 80 and 100 min to 72 and 77% above baseline, respectively, $F(1) = 6.21$, $p = 0.03$; $F(1) = 9.02$, $p = 0.01$. Also, significant time × treatment interactions were found between the saline and 0.5-g/kg ethanol-stress treatment groups, $F(5) = 3.63$, $p = 0.007$, and a significant effect of time was found between the 0.5-g/kg ethanol alone and 0.5-g/kg ethanol-stress treatment groups, $F(5) = 4.44$, $p = 0.002$.

Extracellular DOPAC was not significantly affected when 2 g/kg ethanol was given to resting rats (Fig. 5). However, a profound effect on DOPAC during stress was seen if 2 g/kg ethanol were administered before immobilization. Extracellular DOPAC peaked at 100% over baseline during the first 20 min after stress. In this group, DOPAC was significantly greater than saline controls at 60, 80, and 100 min and there was a significant time × treatment interaction, $F(5) = 6.99$, $p = 0.0001$, between the two groups. Two g/kg ethanol ap-

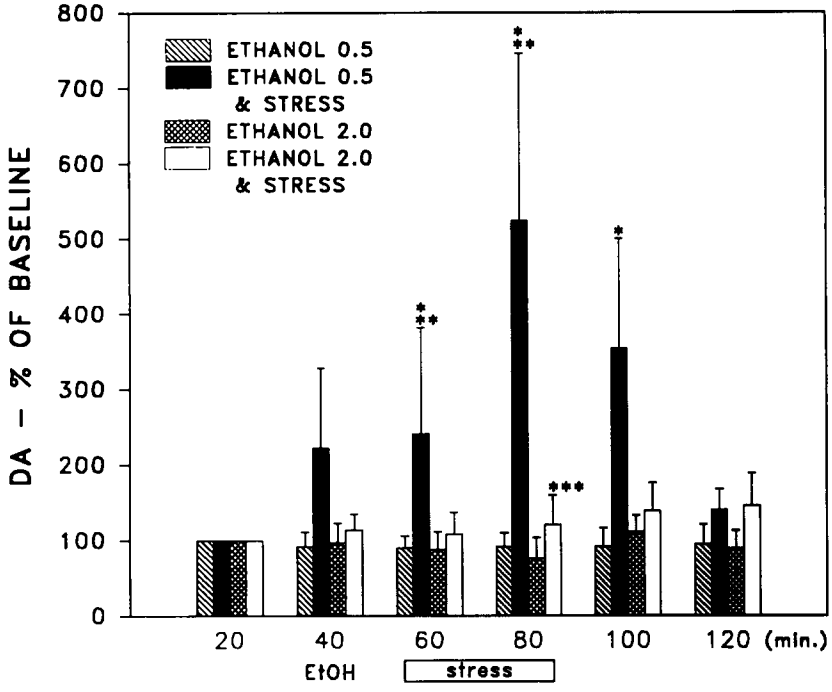

FIG. 3. Effect of 0.5 and 2 g/kg IP ethanol in resting and/or stressed rats on cortical dopamine (DA). Results are expressed as the mean ± SEM percent variation of the prestress value. $*p < 0.04$ vs. ethanol 0.5; $**p < 0.04$ vs. ethanol 2.0; $***p < 0.009$ vs. ethanol 0.5 and stress.

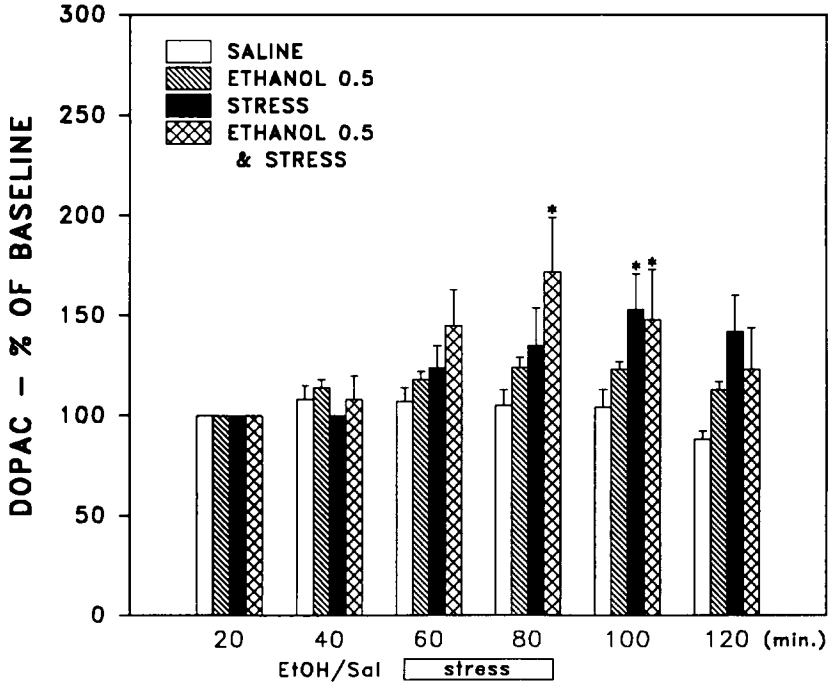

FIG. 4. Effect of 0.5 g/kg IP ethanol in resting and/or stressed rats on cortical dihydroxyphenylacetic acid (DOPAC). Results are expressed as the mean ± SEM percent variation of the prestress value. $*p < 0.04$ vs. saline.

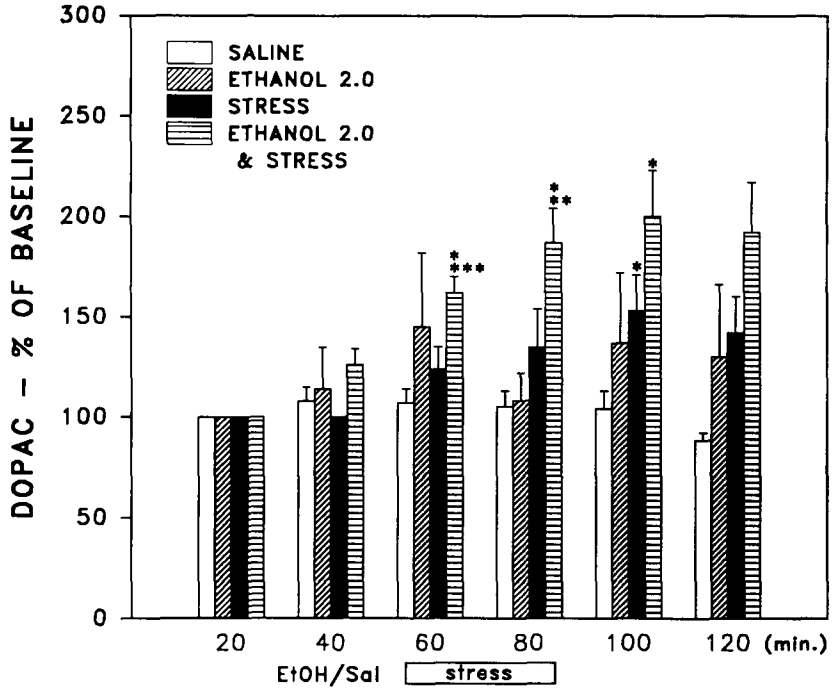

FIG. 5. Effect of 2 g/kg IP ethanol in resting and/or stressed rats on cortical dihydroxyphenylacetic acid (DOPAC). Results are expressed as the mean ± SEM percent variation of the prestress value. *$p < 0.04$ vs. saline; **$p < 0.02$ vs. ethanol 2.0; ***$p < 0.02$ vs. stress.

pears to potentiate stress-induced increases in DOPAC, even though the combined treatment was only significantly greater than stress alone at 60 min, $F(1) = 7.11$, $p = 0.02$. Also, the 2-g/kg ethanol-stress combination produced larger increases in DOPAC than those seen with the high dose of ethanol alone. A significant time × treatment interaction was found between these two groups, $F(5) = 2.42$, $p = 0.05$, and extracellular DOPAC was significantly greater than ethanol alone at 100 min after the ethanol-stress combination, $F(1) = 7.34$, $p = 0.02$.

A comparison of the two doses of ethanol on extracellular DOPAC is shown in Fig. 6. There was virtually no difference between the effects of the high and low doses of ethanol alone on DOPAC. Similarly, the effect of the 0.5-g/kg ethanol-stress treatment on DOPAC was not significantly different from the effect of the 2-g/kg ethanol-stress treatment, even though it appears that the effect of the high dose of ethanol may have lasted somewhat longer (Fig. 6).

DISCUSSION

Immobilization stress for 40 min caused marked changes in extracellular DA in the frontal cortex, possibly due to enhanced release of the neurotransmitter. This confirms previous microdialysis studies that have shown that activation of the mesocortical DA system by a stressor will increase extracellular DA in the cortex (1,21,22). The effect of stress on cortical DA was striking but brief. DA levels reached their maximum after 40 min of immobilization and returned to previous baseline levels within 20 min of termination of the stressor. Imperato et al. (22) found a second increase in cortical DA after release from 2 h of restraint but this effect may have been due to the longer duration of restraint.

A low dose of ethanol (0.5 g/kg) did not alter basal levels of DA. Nevertheless, 0.5 g/kg ethanol has been shown to induce a syndrome of behavioral stimulation (20). This dose also did not significantly affect stress-induced increases in DA. However, a wide range of responses was observed in rats that received 0.5 g/kg ethanol prior to stress and it appears that this dose of ethanol might have actually enhanced the effect of stress on extracellular DA in some animals. Thus, it is likely that such a low dose of ethanol affects animals individually to different degrees.

Similarly, a 2-g/kg dose of ethanol did not alter basal levels of DA in our study. However, it did dramatically reduce stress-induced increases in DA. Because ethanol does not affect basal DA in resting animals, it probably does not directly block DA release but it may be acting through an indirect effect on the mesocortical dopamine system. Electrophysiological (29,36) and behavioral (18,26,32) studies have shown that high doses of ethanol can enhance GABAergic transmission, the putative mechanism of action of benzodiazepines and ethanol. Thus, an acute dose of ethanol could reduce stress-induced changes in DA through a facilitation of inhibitory neurotransmission without affecting basal DA levels directly. The significant differences between the effects of the low and high doses of ethanol may be indicative of a dose-response effect of ethanol on GABAergic transmission, that is, a low dose of ethanol, in this case 0.5 g/kg, may not be able to enhance GABAergic transmission to such an extent that sedation will occur, whereas a higher dose of ethanol can enhance GABAergic transmission to a degree that sedation occurs and reduces the response to stress in the frontal cortex.

Although acute ethanol treatment did not affect basal DA levels, we have reason to believe that ethanol can effect extracellular DOPAC. In this study, 0.5 g/kg ethanol did have a

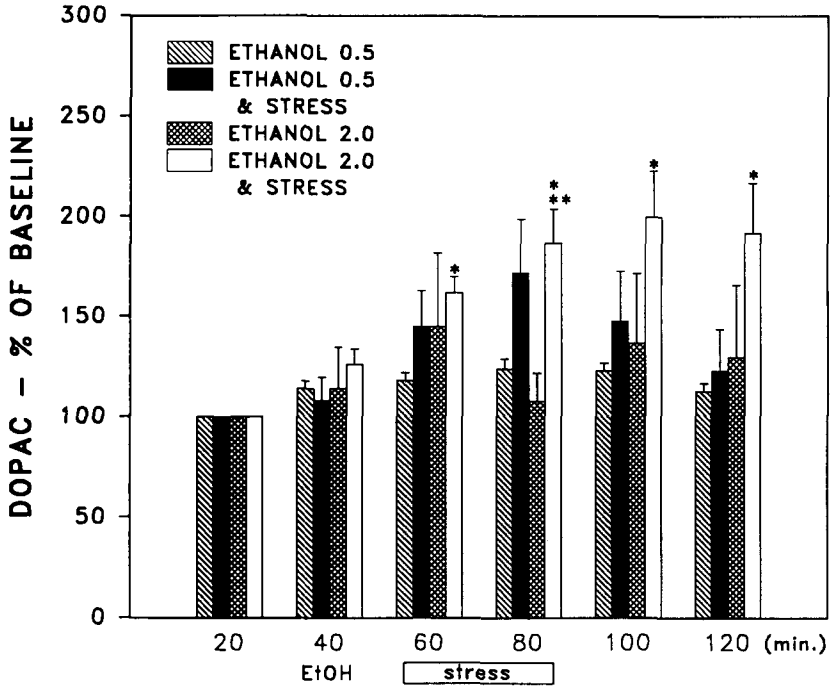

FIG. 6. Effect of 0.5 and 2 g/kg IP ethanol in resting and/or stressed rats on cortical dihydroxyphenylacetic acid (DOPAC). Results are expressed as the mean ± SEM percent variation of the prestress value. *$p < 0.005$ vs. ethanol 0.5; **$p < 0.02$ vs. ethanol 2.0.

slight effect on DOPAC reflected in a significant time effect vs. saline treatment. It also appears that 2 g/kg ethanol elevated DOPAC levels to some extent although this effect was not statistically significant. However, in a second group of eight rats that received 2 g/kg ethanol under the same conditions as those reported here we did see a significant increase in extracellular DOPAC after acute treatment with ethanol [100 ± 5.4, 142 ± 12.1, 140 ± 11.2, 153 ± 10.1, 152 ± 16.7, 143 ± 12.6, 131 ± 12.2 (% age of baseline ± SEM); time × treatment interaction, $F(15) = 3.45$, $p = 0.0001$]. This increase in DOPAC is also supported by a number of other studies that have found similar increases in cortical (8) and striatal (10,13,20,23) DOPAC after acute ethanol treatment. Therefore, we believe that we may have seen a particularly broad range of individual responses in these rats that, when averaged, diluted the effect of the high dose of ethanol on DOPAC. Because a change in DA was not observed and a slight increase in DOPAC was noted, this finding might indicate that levels of DOPAC may not solely reflect transmitter release and activity and, as a result, would not be a reliable index of DA release (35,41). Several studies have shown that acute administration of ethanol can increase the activity of monoamine oxidase (MAO), the enzyme that catabolizes DA to DOPAC, in vivo (2,25,33). In this case, ethanol may have stimulated MAO, which in turn increased the production and release of DOPAC. Also, ethanol has been shown to increase the activity of tyrosine hydroxylase (5). It is possible that ethanol enhanced the activity of tyrosine hydroxylase, thereby increasing the synthesis and intraneuronal metabolism of DA and leading to the accumulation of DOPAC. Thus, the increase in DOPAC may have been dependent upon the stimulation of enzymes and unrelated to changing levels of extracellular DA.

DOPAC also increased as a result of immobilization but its onset was delayed and its time course protracted relative to the increase in DA. In this case, the increase in DOPAC might have been due to catabolism of the DA released during stress after its reuptake into the nerve terminal (3). When 0.5 g/kg ethanol was administered prior to immobilization, DOPAC increased approximately the same percentage over baseline levels as that of stress alone but the increase peaked 20 min earlier. This increase in the rate of DA metabolism might have been due to the activation of MAO and/or tyrosine hydroxylase described above. One of the most striking results in this study was the effect of 2 g/kg ethanol and stress on extracellular DOPAC. Both of these treatments when administered individually increased DOPAC slightly, with stress having a more pronounced effect. However, when 2 g/kg ethanol was administered prior to stress the two treatments had an additive effect on increases in extracellular DOPAC. This finding is in contrast to our results for DA in which the high dose of ethanol antagonized stress-induced increases in extracellular DA. Thus, even though it appears that ethanol can antagonize the effects of stress on DA release it might not alter the effects of stress on DOPAC production. This result also implies that stress and ethanol may exert their effects on DOPAC through two separate mechanisms of action. In this case, ethanol may influence either MAO or tyrosine hydroxylase or both and is increasing DOPAC via an intracellular mechanism that is independent of changing extracellular DA levels. But, immobilization might also be increasing DOPAC through a mechanism that is independent of changes in extracellular DA. We demonstrated that even though DA release is antagonized by 2 g/kg ethanol part of the observed stress-induced increase in DOPAC after the 2-g/kg ethanol-stress treatment must be due to stress. One explanation for this finding may be that

ethanol can enhance the reuptake of dopamine into the nerve terminal to such an extent that any changes in extracellular DA are quickly attenuated. Thus, because of our long sampling time (20 min) we were unable to detect any brief, stress-induced changes in DA although we could still detect the corresponding increase in DOPAC resulting from reuptake of the released DA. This explanation is unlikely, though, because the absolute amount of extracellular DOPAC extruded after immobilization does not account for the considerably greater amount of DA released during immobilization. Therefore, it is probably an oversimplification to assume that stress-induced increases in DOPAC are strictly due to the catabolism of DA released during immobilization. If stress-induced increases in DOPAC do not necessarily result from DA release, some other mechanism must account for its increase in the absence of a corresponding change in extracellular DA. It is possible that stress stimulates DOPAC production through an intracellular mechanism such as increased synthesis of dopamine that could not be elucidated with our experimental protocol. This assumption also supports the conclusion that changes in metabolites may reflect cellular processes and are not necessarily an index of transmitter release (35,41).

Stress is often implicated in the initiation and continuation of alcohol consumption and there is a growing body of evidence that may indicate a physiological interaction between ethanol and stress (30,31). Ethanol has been shown to eliminate sound-induced seizures (11,17), normalize behavior in a conflict situation (9), reverse the effects of stress on brain and plasma monoamines (12,14,15,24), and restore normal locomotor activity after stress (39). Also, stress has been shown to increase voluntary intake of ethanol (27,34,40). However, there are reports that contradict these findings (30). Our studies clearly indicate that there is an interaction of ethanol and stress in the mesocortical DA system. It is possible that the increase in extracellular DA in the frontal cortex during stress is a characteristic of stress-induced anxiety. Thus, ethanol may be exerting an sedative or anxiolytic effect by antagonizing and eliminating this increase in extracellular DA. But, there are reports that contradict this conclusion (22). Another explanation may be that ethanol, in higher doses, can enhance GABAergic neurotransmission and produce sedation and anxiolysis indirectly. This upholds the tension-reduction hypothesis of alcohol consumption because ethanol would be able to cause sedation or reduce anxiety through a GABAergic mechanism similar to benzodiazepines, which have been shown to reduce anxiety and tension. Our data support this conclusion. A third interpretation is that increases in DA counteract adverse effects of stress (14,21). Activation of dopaminergic systems are often implicated in the rewarding and reinforcing properties of drugs of abuse, including alcohol. If dopamine is released to counteract stress, our finding that a low dose of ethanol potentiates DA release supports this conclusion. This result also supports the tension-reduction hypothesis of ethanol because the initial intake of ethanol, that is, a low dose, would counteract stress and possibly lead to further alcohol consumption. Unfortunately, we cannot yet determine which of these explanations describes the interaction of ethanol and stress in the dopaminergic system.

We found that 40 min of immobilization stress significantly increases extracellular DA and DOPAC in the frontal cortex of the rat. A low dose of IP-administered ethanol (0.5 g/kg) does not change levels of DA and DOPAC in resting rats but potentiates the effects of stress on DA. A high dose of ethanol (2 g/kg) also may or may not have any significant effects in resting animals but it significantly antagonizes stress-induced increases in DA while it has an additive effect on stress-induced increases in DOPAC.

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